which shall be considered the filing date for purposes of the act.

Interested persons may submit relevant information on the application to the Dockets Management Branch (address above) in two copies (except that individuals may submit single copies) and identified with the docket number found in brackets in the heading of this document. These submissions may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

The agency encourages any person who submits relevant information on the application to do so by April 17, 1995, and to provide an additional copy of the submission directly to the contact person identified above, to facilitate consideration of the information during the 30-day review period.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (sec. 802 (21 U.S.C. 382)) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10) and redelegated to the Center for Veterinary Medicine (21 CFR 5.44).

Dated: March 24, 1995.

Robert C. Livingston,

Director, Office of New Animal Drug Evaluation, Center for Veterinary Medicine.

[FR Doc. 95–8451 Filed 4–5–95; 8:45 am]

BILLING CODE 4160–01–F

[Docket No. 95D–0052]

Changes To Be Reported for Product and Establishment License Applications; Guidance

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is issuing a guidance document entitled ''Changes to be Reported for Product and Establishment License Applications; Guidance.'' The guidance document is intended to provide manufacturers of licensed biological products guidance on changes in manufacturing procedures and establishments which may be implemented with and without prior approval by the Director, Center for Biologics Evaluation and Research (CBER). This document does not apply to manufacturers of Whole Blood, blood components, Source Leukocytes, and Source Plasma, and it does not address labeling changes. By following this guidance document, manufacturers of licensed biologicals may, in some instances, reduce their reporting burden and facilitate implementation of certain changes.

DATES: Written comments may be submitted at any time.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, rm. 1–23, 12420 Parklawn Dr., Rockville, MD 20857. Comments should be identified with the docket number found in brackets in the heading of this document. Two copies of any comments are to be submitted except that individuals may submit one copy. A copy of the guidance document and received comments are available in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

FOR FURTHER INFORMATION CONTACT: Stephen M. Ripley, Center for Biologics Evaluation and Research (HFM–635), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852–1448, 301–594–3074.

SUPPLEMENTARY INFORMATION: Under § 601.12 *Changes to be reported* (21 CFR 601.12), manufacturers are required to report important proposed changes in location, equipment, management and responsible personnel, or in manufacturing methods and labeling, of any product for which a license is in effect or for which an application for license is pending, to the Director, CBER. Such reports are to be filed by the manufacturer not less than 30 days in advance of the time that such changes are intended to be made except in case of an emergency. Proposed changes in manufacturing methods and labeling may not become effective until notification of acceptance is received from the Director, CBER.

Reporting changes under § 601.12 represents a significant workload for the industry and the agency. In addition, regulated industry has expressed concern about delays in implementing changes and inconsistencies in reporting requirements for product license applications (PLA's), establishment license applications (ELA's), and new drug applications (NDA's). To reduce the reporting burden on manufacturers of biological products and to facilitate the approval process, FDA is issuing this guidance document, which describes CBER's current interpretation of § 601.12(a) and (b).

The guidance document is not intended to affect the reporting requirements currently specified in § 601.12, but to provide clarifying descriptions of the types of changes that are currently considered to be ''important'' within the meaning of that section. In addition, the document clarifies the types of changes which may be implemented 30 days after submission of a supplement and those which must await approval of a supplement prior to implementation. Thus, the guidance document outlines three categories for reporting changes, based on the importance and nature of the changes. The document lists examples of changes that would fall into each category.

This document does not apply to changes in manufacturing processes and facilities associated with the manufacture of Whole Blood, blood components, Source Leukocytes, or Source Plasma. CBER is currently evaluating reporting requirements in those areas. In addition, the guidance document does not address labeling changes. However, in the **Federal Register** of August 3, 1994 (59 FR 39570), FDA published a notice of availability for the revised Office of Establishment Licensing and Product Surveillance Advertising and Promotional Labeling Staff (APLS) Procedural Guidance Document. The APLS Procedural Guidance document details the approach that manufacturers and distributors should follow in submitting advertising and promotional material for review by CBER. The APLS Procedural Guidance Document also provides guidance on CBER's current interpretation of § 601.12 as it applies to reporting important proposed changes in labeling; specifically, promotional labeling of biological products for which a license is in effect or for which an application for a license is pending.

As with other guidance documents, FDA does not intend this document to be all inclusive. The document is intended to provide information and does not set forth requirements. Manufacturers may follow the guidance or may choose to use alternative procedures even though they are not provided in this document. If a manufacturer chooses to use alternative procedures, that manufacturer may wish to discuss the matter further with CBER to prevent expenditure of resources on activities that FDA may later determine to be unacceptable.

This guidance document is not binding on either FDA or licensed manufacturers of biological products and does not create or confer any rights, privileges, or benefits for or on any person.

Interested persons may submit to the Dockets Management Branch (address above) written comments on the guidance document. Received comments will be considered to determine if further revision to the guidance document is necessary.

The text of the guidance document follows:

Food and Drug Administration, Center for Biologics Evaluation and Research (CBER), Changes to be Reported for Product and Establishment License Applications; Guidance

I. Introduction and Background

A significant number of supplements to approved biological product and establishment license applications submitted to CBER during an average year involve changes which fall under § 601.12 *Changes to be reported* (21 CFR 601.12).

Under this regulation, important proposed changes in location, equipment, management and responsible personnel, or in manufacturing methods and labeling, are required to be reported to CBER not less than 30 days in advance of the time such changes are intended to be made (§ 601.12(a)). Proposed changes in manufacturing methods and labeling may not become effective until notification of acceptance is received from the Director, CBER (§ 601.12(b)).

This document is not intended to affect the reporting requirements in § 601.12, but to provide clarifying descriptions of those requirements. This guidance does not apply to manufacturers of Whole Blood, blood components, Source Leukocytes, and Source Plasma. Guidance on reporting requirements in those areas is currently under evaluation within CBER. In addition, this document does not address labeling changes. For guidance on the submission of advertising and promotional material, see the Office of Establishment Licensing and Product Surveillance Advertising and Promotional Labeling Staff (APLS) Procedural Guidance Document (August 1994).

To facilitate the approval process, CBER performed a review of the types of changes being reported and assessed the relative impact of each change on product purity, potency, and safety. Results of this analysis have provided CBER the rationale for describing three categories of changes based on potential effect on product safety, purity, and potency, with each category associated with a different notification mechanism. In general, the types of changes for which CBER recommends less stringent reporting represent changes which, for the most part, have not been associated with demonstrable effects on product purity, potency, or safety, and/or which are readily amenable to on-site scrutiny during inspection of the production facility. In many instances, manufacturers will need to evaluate changes addressed in the three categories using validated standard operating procedures (SOP's) or specifications.

Regardless of whether a supplement is required to be filed, the manufacturer in making such changes must conform to the current good manufacturing practice (CGMP) requirements of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 351(a)(2)(B)) and the regulations in 21 CFR parts 210 and 211. Changes affecting the method of manufacture require validation under the CGMP regulations. In addition, manufacturers must comply with the recordkeeping requirements under the CGMP regulations and ensure that relevant records are readily available for FDA inspection.

This document identifies and categorizes the types of changes in manufacturing processes and establishments which may be implemented with and without prior approval by CBER.

This guidance document is not binding on either FDA or licensed manufacturers of biological products and does not create or confer any rights, privileges, or benefits for or on any person. It does, however, describe CBER's current interpretation of § 601.12. Where this document reiterates a requirement imposed by statute or regulation, the force and effect as law of the requirement is not changed in any way by virtue of its inclusion in this document.

Section A of this document contains general definitions of each category of change as it pertains to notification or reporting requirements outlined in § 601.12(a) and (b). This section also defines a Periodic Report for Category I changes. Section B of this document provides instruction on sending submissions to CBER. Section C of this document augments these definitions with selected examples of modifications appropriately falling under each category. Section D of this document contains guidance on categorizing proposed changes which may not be listed in section C. Section E of this document discusses the kind of information the agency is asking manufacturers to submit in a Periodic Report.

II. Guidance and Rationale

A. Definitions

General definitions of each category of reporting changes are as follows:

1. Category I—Change(s) for Which No Supplement Submission is Required and Which May be Described in a Periodic Report

This category includes modifications to procedures, process parameters, components, manufacturing methods, reagents, equipment and facilities which do not rise to the level of the ''important'' changes required to be reported under § 601.12. These are changes that are designed to tighten control on the production process, or have not been associated with adverse impact on product safety, purity or potency. Manufacturers should qualify and, as necessary, validate such changes before implementing them. These changes should be shown not to affect the integrity of the product. For this category, the manufacturer generates and retains all relevant data defining (and, as necessary, validating) changes which are implemented. In order to expedite the agency's review of changes, such data should be readily accessible for FDA-establishment inspections. The agency recommends that the firm notify CBER in a Periodic Report (see description below) of the changes and dates of implementation.

2. Category II—Change(s) Requiring a Supplement Submission and Which May be Implemented Prior to CBER Approval

This category includes modifications to location, equipment, management, and personnel that do not change manufacturing methods, but have the potential to adversely affect product safety, purity, and potency. For these changes, the manufacturer should submit a standard supplement, accompanied by all relevant supporting data, with a request to implement not less than 30 days following the supplement's receipt by CBER's Document Control Center. Such supplements should be clearly marked ''Category II Supplement, Changes to be Implemented'' at the top of the cover letter. CBER will confirm the submission and its receipt date in the reference number assignment letter. CBER intends to follow relevant application review policies in assigning supplement review.

CBER will process Category II changes as establishment or product license application supplements and will take official action on such supplements on, before, or after this 30-day period. If CBER officials do not contact the sponsor via telephone or written correspondence within 30 days following the documented receipt date to question or reject the ''Category II'' status, the manufacturer may implement the change. CBER may communicate with the firm during this 30 day period for clarification or to advise that the change is considered to be a Category III supplement (see description below).

Manufacturers should be aware that Category II changes are implemented subject to agency approval. The agency may refuse to approve a supplement for a change that has already been implemented. In assessing a manufacturer's plans to correct a problem, the agency intends to consider the manufacturer's reasons for making the change and the alternatives available to the manufacturer, among other things. If the circumstances warrant, the agency may require the change to be immediately discontinued. When circumstances permit, it is FDA's intent to allow manufacturers to correct a problem with minimal expense and without unnecessary waste.

3. Category III—Change(s) Which Require CBER Approval Prior to Implementation

This category includes changes in manufacturing methods and requires manufactures to submit all relevant supporting documentation and await CBER's approval prior to implementation. As with Category II submissions, CBER intends to follow relevant application review policies in assigning supplement review.

4. Periodic Reports

A Periodic Report is a voluntary written report submitted every 6 months listing and briefly describing Category I changes and providing the date of implementation of such changes. Reports should include separate descriptions of EACH change affecting a licensed product and should identify for each change the specific establishment location involved. (See section E of this document for requested information.)

B. Where to Submit Supplements and Periodic Reports

Three copies of all supplements and periodic reports should be submitted to the Center for Biologics Evaluation and Research (HFM–99), Food and Drug Administration, 1401 Rockville Pike, suite 200N, Rockville, MD 20852–1448.

C. Selected Examples

1. Category I

CBER currently considers the following examples to be changes that will not ordinarily rise to the level of the ''important'' changes required to be reported under § 601.12. These changes need not be submitted to CBER prior to implementation and may be submitted in a periodic report as ''Category I changes.'' This listing provides representative samples of Category I changes and is not all inclusive.

i. Change in purchasing source of approved final fill components (stoppers, vials, seals) that meet established specifications. This does not include change(s) in composition of such components or suppliers of ancillary chemicals and drug products such as diluents.

ii. Change in harvesting and/or pooling procedures which does not affect method of manufacture, recovery, storage conditions, sensitivity of detection of adventitious agents, or production scale; e.g., collection in smaller quantities to improve process efficiency.

iii. Changes in cell inoculum; e.g, mode of expansion (attached versus suspension; bioreactor versus spinner), cell density, staging of culture. This excludes viral products; e.g., vaccines and in vitro diagnostic kits.

iv. Change in storage conditions of reference standard or panel based on stability data generated with an FDA-approved protocol.

v. Extension of dating period for in-house reference standards, based on real-time data, according to an FDA-approved protocol.

vi. Replacement of inhouse reference standard or reference panel (or panel member) according to FDA-approved standard operating procedures (SOP's) and specifications.

vii. Tightening of specifications for reference standard or lot release analyses.

viii. Establishment of new Working Cell Bank derived from previously approved Master Cell Bank according to an FDA-approved SOP.

ix. Narrowing (tightening) of specifications for intermediates and endproducts to provide greater assurance of product purity and potency.

x. Use of alternative storage containers for intermediates, with no change in sterility, depyrogenation status, or composition of container.

xi. Change in storage conditions of inprocess intermediates based on data from an FDA-approved stability protocol (labeling not affected).

xii. Change in bulk pool size for formulation without process scale-up.

xiii. Batch size changes for ancillary components (specimen diluents, positive and/or negative controls, substrate buffers, etc.) where all equipment contact surfaces remain chemically identical to approved equipment.

xiv. Change in the number of vials per fill with no scale-up or impact on parameters defined in the environmental assessment.

xv. Change in shipping conditions (e.g., temperature, packaging, custody) based upon data derived from studies following an FDA-approved protocol.

xvi. Rework of biologic product which has failed final release testing using FDA-approved rework protocol. Note: Any lot of product subject to rework should be so noted on the product release protocol.

xvii. Change in stability test protocol to include more stringent parameters; e.g., additional assays, tightened specifications, etc.

xviii. Replacement of equipment with that of identical design and operating principle involving no change in process parameters.

xix. The following modifications of areas not used for production or storage of intermediate or finished product (such as testing laboratories, materials storage, warehouse, employee break areas, etc.):

(a) Addition of outside areas that do not adversely affect the product manufacturing area or utility systems;

(b) Expansion or reorganization of off-site support space that does not affect the product manufacturing areas;

(c) Modification to or relocation of support space within a product manufacturing facility that does not affect plant utility systems and flow patterns, or adversely affect product purity or environmental conditions (e.g., addition of half partitions or benches).

xx. The relocation of equipment within appropriate areas of approved facilities, not increasing risk to product purity or integrity of testing (e.g., relocation of fermentor in fermentation suite).

xxi. Upgrade in air quality, material, or personnel flow where product specifications remain unchanged. Involves no change in equipment or physical structure of production area.

xxii. Changes in personnel other than the Responsible Head (21 CFR 600.10) or individuals serving in a capacity of alternative or temporary Responsible Head.

2. Category II

CBER currently considers the following examples to be ''important'' proposed changes in location, equipment, management and responsible personnel. These changes must be reported pursuant to § 601.12(a) and meet the definition of a ''Category II Supplement.'' This listing provides representative samples of Category II changes and is not all inclusive.

i. Addition of back-up systems for manufacturing processes which are identical to the primary system and serve as an alternate resource (not expansion of capacity) within an approved production area.

ii. Upgrade to production air handling or water systems using like equipment and not affecting established specifications; e.g., removal of dead legs in water for injection (WFI) system. (Does not include replacement of parts or routine repair and maintenance (Category I).)

iii. Replacement of equipment with that of similar, but not identical, design and operating principle that does not affect the process methodology.

iv. Expansion of existing manufacturing support systems (WFI, heating, ventilation, and air-conditioning (HVAC)); e.g., adding an additional WFI loop.

v. Relocation of operations within the same production area of an approved facility with no change in equipment or room classification.

vi. Modification of an approved manufacturing area which does not adversely affect safety, purity or potency of product; e.g., adding new interior partitions or walls to increase control over the environment and replacing or adding new surfaces to enhance cleaning.

vii. Change in Responsible Head (21 CFR 600.10) or individuals serving in a capacity of alternative or temporary Responsible Head.

3. Category III.

CBER currently considers the following examples to be ''important'' proposed changes in manufacturing methods. These changes require CBER approval before they may be implemented under § 601.12(b), and meet the definition of a ''Category III Supplement.'' This listing provides representative samples of Category III changes and is not all inclusive.

i. Establishment of new Master Cell Bank.

ii. Change in inhouse reference standard or reference panel (panel member) resulting in modification of reference specifications.

iii. Establishment of alternate test method for reference standards, release panels, product intermediates, or endproduct.

iv. Replacement of existing test method with new procedure or method; e.g., change from radioimmunoassay (RIA) to enzyme-linked immunosorbent assay (ELISA).

v. Change in process parameters; e.g., growth cycle, chromatographic medium, process time and/or temperature, filtration process.

vi. Change in sequence of processing steps, including addition of processing step; e.g., viral removal or inactivation.

vii. Change in production scale (up or down) involving changes in equipment, process parameters, or process methodology.

viii. Change in chemistry or formulation of solutions used during processing.

ix. Changes in conjugation chemistry or process.

x. Change in composition of the biological product or ancillary components.

xi. Change in dosage form.

xii. Any change which results in detectable relaxing of product specifications and modification in potency, sensitivity, or specificity.

xiii. Change in fill volume (per vial) from an approved production batch size and/or scale.

xiv. Reprocessing of product without a previously approved reprocessing protocol.

xv. Change in stability testing program; e.g., substitution of analytical methods or potency assay, broadening of acceptance criteria, change in storage temperature, change in test algorithm.

xvi. Extension of dating period for intermediate or endproduct.

xvii. Change in storage conditions for licensed final product or intermediate based on real-time data from FDA-approved stability protocol (labeling affected).

xviii. The following changes in manufacturing location that affect process

conditions and thereby have the potential to affect product safety, purity, or potency:

(a) Use of a previously unapproved manufacturing area or facility;

(b) Change in air quality, water quality, material, or personnel flow for licensed product manufacturing areas.

(c) Change from single product manufacturing to multiple product manufacturing using same equipment and/or personnel.

(d) Renovation to physical structure that alters product, material, and/or personnel flow.

xix. Addition to or replacement of an FDA-approved manufacturing step performed under contract to a second facility.

D. Categorization of Proposed Changes

Before implementing a change which is not identified above or does not clearly fit into one of the defined categories, manufacturers should discuss the proposed change with CBER. If guidance is not sought, the change should be reported in the form of a Category III supplement, subject to CBER approval prior to implementation.

Requests for information regarding categorization of proposed changes not included in the above categories may be addressed to the Director of the appropriate applications Division within the Office with assigned product, or establishment, responsibility at the Center for Biologics Evaluation and Research (HFM–99), Food and Drug Administration, 1401 Rockville Pike, suite 200N, Rockville, MD 20852–1448.

E. Information Requested for Category I Periodic Reports

FDA requests that manufacturers submit the following information for each Category I change in the order shown: (1) Name of the manufacturer; (2) the establishment license number; (3) the report dates (time period covered by the report); (4) the product(s) affected (list each one); (5) the change implemented, including: (a) A brief description and reason for the change and/or modification, (b) the establishment location involved, (c) the date the change was implemented, and (d) a cross-reference to the Approved Validation Protocol or Standard Operating Procedure, if applicable; and (6) the signature of the Responsible Head and the date signed.

Dated: March 31, 1995.

William B. Schultz,

Deputy Commissioner for Policy.

[FR Doc. 95–8382 Filed 4–5–95; 8:45 am]

BILLING CODE 4160–01–F

[Docket No. 93F–0201]

Asahi Denka Kogyo K. K.; Withdrawal of Food Additive Petition

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the withdrawal, without prejudice to a future filing, of a food additive petition (FAP 3B4378) proposing that the food additive regulations be amended to provide for the safe use of sodium 2,2′-methylenebis(4,6-di-*tert*-butylphenyl) phosphate as a clarifying agent in polypropylene articles intended for contact with food to include the use at temperatures up to and including retort conditions.

FOR FURTHER INFORMATION CONTACT: Helen R. Thorsheim, Center for Food Safety and Applied Nutrition (HFS–216), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202–418–3092.

SUPPLEMENTARY INFORMATION: In a notice published in the **Federal Register** of July 29, 1993 (58 FR 40656), FDA announced that a food additive petition (FAP 3B4378) had been filed by Asahi Denka Kogyo K. K., c/o Japan Technical Information Center, Inc., 1002 Pennsylvania Ave. SE., Washington, DC 20003. The petition proposed to amend the food additive regulations in § 178.3295 *Clarifying agents for polymers* (21 CFR 178.3295) to provide for the safe use of sodium 2,2′-methylenebis(4,6-di-*tert*-butylphenyl) phosphate as a clarifying agent in polypropylene articles intended for contact with food to include the use at temperatures up to and including retort conditions. Asahi Denka Kogyo K. K. has now withdrawn the petition without prejudice to a future filing (21 CFR 171.7)

Dated: March 22, 1995.

Eugene C. Coleman,

Acting Director, Office of Premarket Approval, Center for Food Safety and Applied Nutrition.

[FR Doc. 95–8515 Filed 4–5–95; 8:45 am]

BILLING CODE 4160–01–F

[Docket No. 94F–0121]

BASF Corp.; Withdrawal of Food Additive Petition

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the withdrawal, without prejudice to a future filing, of a food additive petition (FAP 3B4384) proposing that the food additive regulations be amended to provide for the safe use of hydroxypropyl acrylate and butanediol diacrylate as monomers in the production of acrylic polymers intended for use in food packaging adhesives.

FOR FURTHER INFORMATION CONTACT: Diane E. Robertson, Center for Food Safety and Applied Nutrition (HFS–216), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202–418–3089.

SUPPLEMENTARY INFORMATION: In a notice published in the **Federal Register** of April 25, 1994 (59 FR 19730), FDA announced that a food additive petition (FAP 3B4384) had been filed by BASF Corp., 9401 Arrow Point Blvd., suite 200, Charlotte, NC 28273. The petition proposed to amend the food additive regulations in § 175.105 *Adhesives* (21 CFR 175.105) to provide for the safe use of hydroxypropyl acrylate and butanediol diacrylate as monomers in the production of acrylic polymers intended for use in food packaging adhesives. BASF Corp. has now withdrawn the petition without prejudice to a future filing (21 CFR 171.7).

Dated: March 22, 1995.

Eugene C. Coleman,

Acting Director, Office of Premarket Approval, Center for Food Safety and Applied Nutrition.

[FR Doc. 95–8516 Filed 4–5–95; 8:45 am]

BILLING CODE 4160–01–F

Health Care Financing Administration

[BPO–130–N]

Medicare and Medicaid Programs; Quarterly Listing of Program Issuances and Coverage Decisions—Fourth Quarter 1994

AGENCY: Health Care Financing Administration (HCFA), HHS.

ACTION: Notice.

SUMMARY: This notice lists HCFA manual instructions, substantive and interpretive regulations and other **Federal Register** notices, and statements of policy that were published during October, November, and December of 1994 that relate to the Medicare and Medicaid programs. Section 1871(c) of the Social Security Act requires that we publish a list of Medicare issuances in the **Federal Register** at least every 3 months. Although we are not mandated to do so by statute, for the sake of completeness of the listing, we are including all Medicaid issuances and Medicare and Medicaid substantive and interpretive regulations (proposed and final) published during this timeframe. We are also providing the content of revisions to the Medicare Coverage Issues Manual published between October 1 and December 31, 1994. On August 21, 1989, we published the content of the Manual (54 FR 34555) and indicated that we will publish